The Central Role of Neutrophil Gelatinase–Associated Lipocalin in Cardiovascular Fibrosis

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A ccumulating evidence indicates that aldosterone plays a predominant role in the pathobiology of cardiopulmonary vascular fibrosis. Mineralocorticoid receptor activation disrupts normal vessel architecture by promoting collagen and elastin degradation, as well as deposition of newly synthesized collagen, which has attendant consequences for both vascular structure and function. The clinical relevance of this concept is supported by epidemiological studies that have shown that vascular stiffness occurs before hypertension and link increased serum aldosterone levels to incident hypertension.1,2 Further support for this concept is found in selected patient populations, including patients with primary aldosteronism, congestive heart failure, and obesity, where evidence of mineralocorticoid receptor activation is associated with circulating markers of fibrosis and increased collagen turnover.3-5 Although these studies provide a framework to explore the association between aldosterone and fibrosis, arterial stiffness, and hypertension, they do not inform on the critical molecular mechanisms or relevant signaling pathways that initiate collagen synthesis and ultimately lead to vascular fibrosis.

In this issue of Hypertension, Tarjus et al6 provide compelling evidence that neutrophil gelatinase–associated lipocalin (NGAL), or lipocalin-2 (Lcn2), is a key mediator of mineralocorticoid-stimulated vascular fibrosis. They convincingly show that NGAL/Lcn2 is associated with aldosterone levels and markers of collagen metabolism in nonhypertensive asymptomatic individuals with abdominal obesity. The authors also provide mechanistic insight to support the central role of Lcn2 by conducting studies in Lcn2 conditional knockout mice using the uninephrectomy/aldosterone infusion/salt model. Under these conditions, absence of Lcn2 expression is associated with lower blood pressure, less oxidant stress, and decreased vascular fibrosis compared with controls. Thus, these studies identify NGAL/Lcn2 as a unifying regulator of aldosterone-stimulated collagen metabolism and vascular fibrosis.

The mechanism(s) by which NGAL/Lcn2 modulates vascular fibrosis is likely multifactorial. NGAL/Lcn2 binds matrix metalloproteinase (MMP)-9 via a disulfide bond, which may function as a redox switch, and is detectable in the circulation. This also suggests that one function of NGAL/Lcn2 is to deliver MMP-9 to sites of vascular remodeling. Studies performed in heart failure models found that in addition to MMP-9, NGAL/Lcn2 physically associates with MMP-2 in the heart, but not skeletal muscle, indicating that this interaction achieves greater importance at sites of tissue injury.7 Although the authors were unable to study this phenomenon owing to structural differences between human and murine Lcn2 (eg, murine Lcn2 does not form a disulfide bond with MMP-9), it does raise the possibility that NGAL/Lcn2 regulates fibrosis through an interaction with other pro or antifibrotic proteins. For example, Lcn2 is known to bind and negatively regulate the actions of hepatocyte growth factor, which is a recognized antifibrotic peptide.8 NGAL/Lcn2 also binds to other proteins that function as receptors, such as megalin or low-density lipoprotein–related protein 2, to facilitate endocytosis of NGAL/Lcn2 and other cargo proteins.9 This is possible as megalin has been associated with fibrogenesis.10 Whether or not fibrosis resulted directly from NGAL/Lcn2 signaling remains to be determined (Figure).

The finding of decreased blood pressure in Lcn2 knockout mice despite challenge with uninephrectomy/aldosterone infusion/salt is not surprising, and there is precedent for this observation. In wild-type mice, high-fat feeding led to an increase in deposition of NGAL/Lcn2 in arteries and an increase in blood pressure, an effect that was not observed in high fat fed Lcn2 knockout mice. This was attributed to the state of polyamination of NGAL/Lcn2. The presence of this post-translational modification of NGAL/Lcn2 is regulated, in part, by adipose tissue, which deamidates NGAL/Lcn2. This results in increased time in the circulation and vascular accumulation. Moreover, studies performed with human NGAL/Lcn2 showed that mutation of cysteine87 to alanine resulted in less polyamines, increased resident time in the circulation, and endothelial dysfunction.11 It is known that aldosterone induces adipose tissue dysfunction suggesting that aldosterone may indirectly promote NGAL/Lcn2 deamidation leading to deposition of NGAL/Lcn2 within the vessel wall and fibrosis. Although NGAL/Lcn2 was not implicated in endothelial dysfunction in this study, this is likely related to the differences between human and murine Lcn2.

Another interesting finding was that uninephrectomy/aldosterone infusion/salt-induced oxidant stress in wild-type but not Lcn2 knockout mice, suggesting that NGAL/Lcn2 regulates the redox milieu. Administration of exogenous Lcn2 to RBE4.1 rat brain endothelial cells has been shown to increase reactive oxygen species levels as early as 3 hours.
activates T helper17+ cells to increase interleukin-17 secretion. It is notable that interleukin-17 upregulates expression of NGAL/Lcn2 directly.15 These observations likely identify NGAL/Lcn2 as the mechanistic link between aldosterone, immune system activation, and fibrosis but do not tell us if these systems operate simultaneously or in sequence.

Taken together, this study identifies NGAL/Lcn2 as an important component of mineralocorticoid-stimulated vascular fibrosis and represents another advance in our understanding of how aldosterone mediates cardiovascular fibrosis. The finding that NGAL/Lcn2, as well as post-translationally modified forms of this protein, can serve as a circulating biomarker is also relevant and may support a putative strategy for the early initiation of mineralocorticoid receptor blockade to limit fibrosis. Furthermore, more in-depth study of the binding partners of NGAL/Lcn2 may highlight other novel targets in this signaling pathway for future therapeutic intervention.

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Disclosures

None.

References


Figure. Mechanisms of neutrophil gelatinase-associated lipocalin (NGAL)-mediated vascular fibrosis. NGAL is polyaminated, which decreases its resident time in the circulation and prevents deposition in the vessel wall. However, NGAL is deaminated under conditions that are associated with elevated levels of aldosterone/mineralocorticoid receptor activation. This, in turn, leads to a decrease in clearance of NGAL from the circulation and increased uptake into the vessel wall. NGAL forms a disulfide bond with matrix metalloproteinase-9 (MMP–9) and facilitates its uptake to promote vascular remodeling. In contrast, NGAL also binds hepatocyte growth factor (HGF) and, thereby, inhibits its profibrotic actions. Within the adventitial layer, aldosterone/mineralocorticoid receptor activation increases the influx of T helper-17 (Th17) cells. These cells secrete interleukin-17 (IL–17), which activates fibroblasts (green cells) to stimulate transcription of NGAL. NGAL is then secreted and can act in an autocrine or paracrine fashion, upregulate galectin-3 (Gal–3), and increase collagen synthesis, deposition, and fibrosis.


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